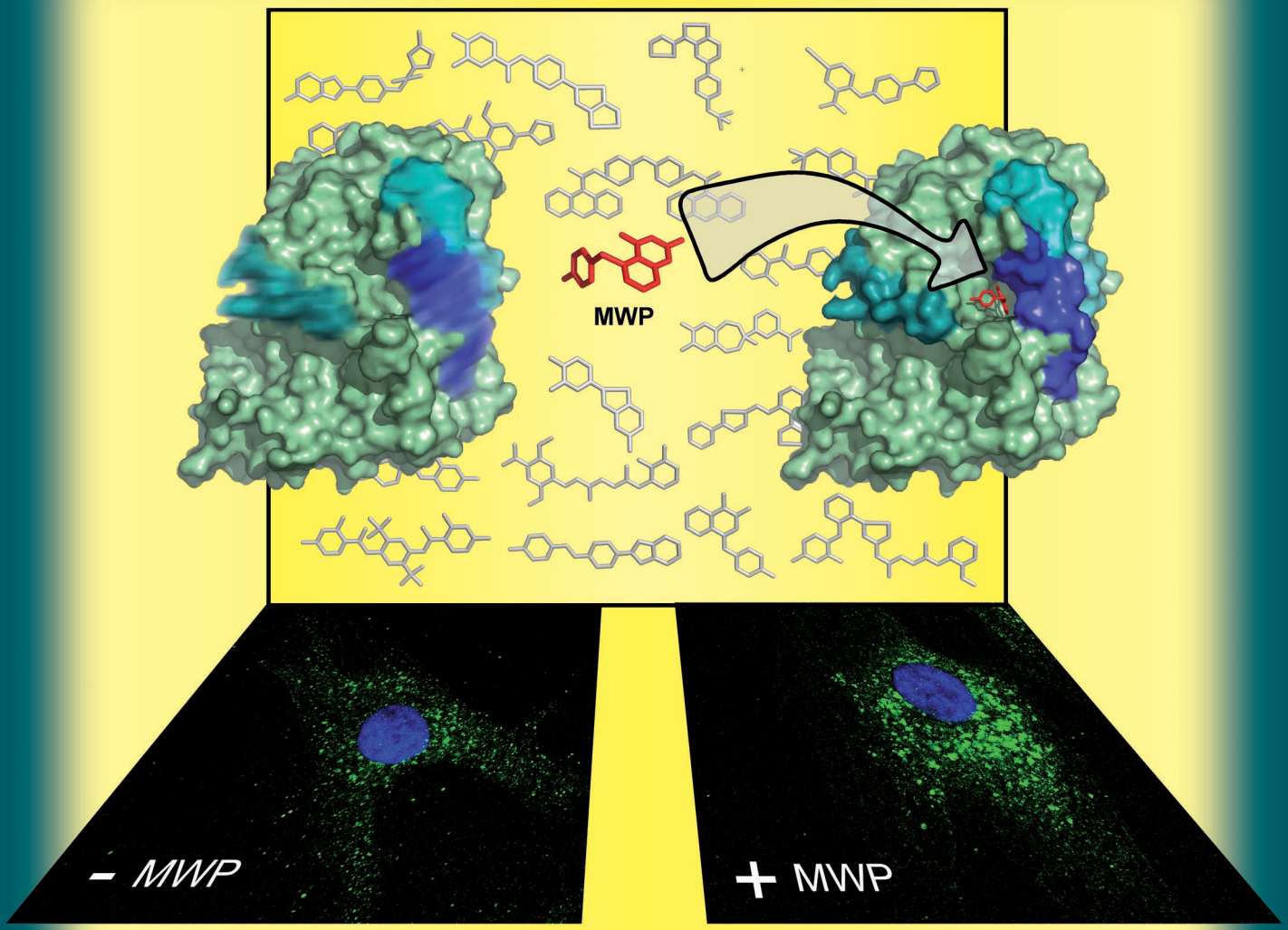
CBCHFX 9 (16) 2549 – 2756 (2008) · ISSN 1439-4227 · Vol. 9 · No. 16 · November 3, 2008

D55712

A EUROPEAN JOURNAL

CHEMBIOCHEM

OF CHEMICAL BIOLOGY



Rigidification of Glucocerebrosidase by Novel Pharmacological Chaperones

16/2008

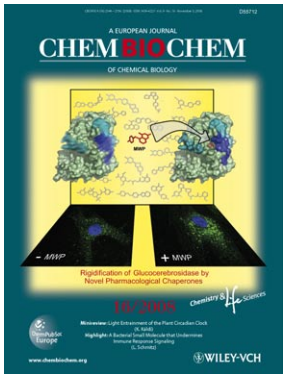
Chemistry & Life Sciences

ChemPubSoc Europe

www.chembiochem.org

WILEY-VCH

Cover Picture



Michael B. Tropak, Gregory J. Kornhaber, Brigitte A. Rigat, Gustavo H. Maegawa, Justin D. Buttner, Jan E. Blanchard, Cecilia Murphy, Steven J. Tuske, Stephen J. Coales, Yoshitomo Hamuro, Eric D. Brown, and Don J. Mahuran*

The cover picture shows the regions (shades of blue) on human lysosomal glucocerebrosidase (green) that undergo a significant reduction in hydrogen–deuterium exchange (denoted by loss of blurriness) upon binding a 2,4-diamino-5-substituted quinazoline (MWP; red). MWP was identified in a high-throughput screen of the Maybridge library of 50 000 small molecule drug-like compounds (grey structures) for inhibitors. The confocal images immediately below the 3D structures of the enzyme are patient fibroblasts homozygous for the common N370S Gaucher disease type I allele, stained with an antibody against glucocerebrosidase (green); these show increased levels of the enzyme in MWP treated (+MWP) cells in comparison with untreated control (−MWP) cells. This study has identified pharmacological chaperones (PC) that are not based on the structure of the glycolipid substrate of the enzyme. These new compounds increase the repertoire of chemical frameworks available for the construction of efficient PCs for the treatment of Gaucher disease. For more details, see the article by M. B. Tropak, D. J. Mahuran et al. on p. 2650 ff.